EXHIBIT NO.

21

Watching Briefs

Report on the 2018 Acute Flaccid Myelitis Outbreaks in the USA

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Abstract

An increase in the number of Acute Flaccid Myelitis (AFM) cases reported in the USA was detected in August 2018. The CDC has confirmed 186 cases of AFM in 2018 making this the largest outbreak of AFM reported in the USA. The cause however remains unknown. In this watching brief we review key features of the current outbreak in context, describe what is known about AFM, and consider probable causes. A two-year epidemic cycle of AFM appears to be emerging, and most current evidence implicates both EV-A71 and EV-D68 as the probable cause of the current outbreak yet key questions remain.

Keywords: Acute Flaccid Myelitis, EV-D68, EV-A71, Outbreak, Epidemiology

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Date of first report of the outbreak	28-Aug-18
Disease or outbreak	Acute Flaccid Myelitis (AFM)
Origin (*country, city, region*)	Multistate, USA
Suspected Source (specify food source,	Non-polio enteroviruses EV-A71 and EV-D68 (,)

zoonotic or human origin or other)	
Date of outbreak beginning	The exact date of outbreak onset is not publicly known. There have been sporadic cases of AFM reported in the US since February 2018, however data provided by the Centres for Disease Control and Prevention (CDC) suggests that an increase in reported AFM cases occurred in late August 2018 (,). Late August as a possible date of outbreak beginning is supported by an October 10th statement from the Washington State Department of Health describing an initial cluster of five AFM cases with symptom onset dated August 28, 2018 ( ). Supporting this, the CDC later confirmed that an increased number of reports for suspected AFM were received with symptom onset dates during August, September, and October ( ).
Date outbreak declared over	N/A - Ongoing as of 28 December 2018.
Affected countries & regions	The CDC is reporting at least 38 US States with confirmed AFM cases reported since the beginning of 2018 ( ). Of the 341 suspected cases reported since February, 186 have been confirmed as of December 28th 2018 ( ). A comprehensive list of states affected with individual counts since February can be seen here: https://www.cdc.gov/acute-flaccid-myelitis/afm-surveillance.html It remains difficult to determine whether state-wise totals reported by the CDC comprise sporadic cases reported prior to late August (the apparent onset of the epidemic wave) or as part of the epidemic. Confirmation of cases reported during the epidemic are also uninformative as large numbers of suspected

	cases could have onset dates between February and August, and individual case data are not described. Public reporting, however, implicates at least seven states in the epidemic wave beginning in late August which could have seeded other states previously reporting sporadic cases prior to August. These include: 1. Washington ( ) (10 confirmed) 2. Illinois ( ) (9 confirmed) 3. Colorado ( ) (16 confirmed) 4. Minnesota ( ) (10 confirmed) 5. New Jersey ( ) (10 confirmed) 6. Pennsylvania ( ) (9 confirmed) 7. Ohio ( ) (12 confirmed)
Number of cases (specify at what date if ongoing)	As of December 28, there have been 341 suspected cases of AFM reported since the beginning of 2018. Only 186 cases have been clinically confirmed, with an unknown number still under investigation. At least half of these confirmed cases have been reported between late August and November 2018 (,).
Clinical features	AFM is a clinical syndrome that principally includes a sudden onset of acute limb weakness or paralysis ( ). Other features of AFM include difficulty breathing, ataxia (unsteady walking), wobbliness, headache, stiff neck, dizziness and jerking movements ( ). Fever can also be expected in 50% of cases ( ). Confirmation of AFM requires clinical evidence of "*acute flaccid limb weakness*" and "*evidence of spinal cord lesions*" within the grey matter as shown by Magnetic Resonance Imaging (MRI) ( ). Evidence of increased white blood cell

count within the Cerebrospinal fluid (CSF) may also be supportive, but not confirmatory, of AFM ( ).

In the current outbreak, the CDC confirmed that 78% of cases confirmed prior to November 2nd (N=62/80) had respiratory symptoms such as cough, runny nose and congestion, 81% (N=65/80) had fever, and 38% (N=30/80) has gastrointestinal symptoms ( ).

AFM as a clinical syndrome may be caused by different pathogens and cannot itself be transmitted from person-to-person. Infectious causes of AFM include polio virus, non-polio enteroviruses EV-A71 and EV-D68 ( ), some flaviviruses, adenoviruses type 21, and some herpesviruses including cytomegalovirus and Epstein-barr virus (, ,). Non-infectious causes may include environmental toxins or genetic disorders ( ).

Mode of transmission (dominant mode and other documented modes)

Transmission of EV-A71 is by the faecal-oral route, however the virus is also present and can transmit via respiratory secretions such as nasal mucus ( ). EV-D68 has only recently been associated with AFM (,), and is primarily transmitted via the respiratory route and respiratory illness is the main clinical syndrome for EV-D68 infection (,). EV-D68 has been detected in faeces of some infected cases but faecal-oral route transmission has not been established like EV-A71 ( ). Both EV viruses can survive on surfaces as fomites (,).

Other known causes of AFM include West Nile, Saint Louis encephalitis, and Japanese encephalitis viruses, which are all

mosquito-borne flaviviruses and are primarily carried by Culex spp. mosquitoes ( ).

Adenovirus transmission is similar to EV-D68, primarily via respiratory secretions. However, unlike EV-D68, transmission via the faecal-oral route has been shown ( ).

Demographics of cases

The exact demographics of all cases in this outbreak are not publicly known. The CDC has reported that among cases confirmed prior to November 2nd, 59% (47/80) were male ( ). The median age of cases is 4 years ( ). This is consistent with the consensus among reporting media indicating that 90% of cases affected are aged under 18 years ( ). In the August-November epidemic wave, all cases in Washington are aged under six years ( ), all cases in Minnesota are under 10 ( ), and all cases in Illinois are under the age of 18 ( ). In Colorado, Pennsylvania, and Ohio, all cases are described among "children" (, ,). There are no details on the cases in New Jersey yet.

Case fatality rate

There has been one suspected death from AFM diagnosed in May 2018, however the CDC has yet to confirm this ( ). In the current epidemic wave, starting in August, no fatalities have been confirmed or reported.

Complications

Mild cases of AFM can expect to fully recover, however at least half of cases may have residual limb weakness requiring ongoing physical therapy ( ). Severe cases of AFM may experience respiratory failure and require ventilator support ( ). Rare neurological complications associated with AFM can sometimes lead to death ( ). Long-term complications include paralysis and residual limb deficits.

Available prevention

The causes of AFM are varied and include both infectious and non-infectious aetiologies. As such, the CDC recommends a variety of prevention strategies including: staying up-to-date with vaccines, basic hygiene i.e. washing your hands, and protecting yourself from mosquito bites (4). Of the known causes of AFM, there are no commercially available vaccines for EV-A71 (18), EV-D68 (11), Saint Louis Encephalitis virus (22) or West Nile virus (23) in the US. A vaccine is available to prevent Japanese Encephalitis virus, however it is only recommended for travellers visiting endemic countries for longer than one-month and not available for infants under two months of age (24).

Available treatment

There is no available treatment for AFM, which is limited to supportive care only. This includes the use of assisted ventilation when necessary (12). Specialists may assist with physical therapy whilst hospitalised to reduce muscle weakness or loss (25). The antiviral Fluoxetine has been trailed as treatment for presumptive EV-D68 associated AFM. However, it was not associated with improved outcomes (26).

Comparison with past outbreaks

In recent times, large outbreaks of AFM were first documented in the US in 2014. In the 2014, 120 cases of AFM were confirmed across 34 states between August and December in the US (10). This AFM outbreak was temporally and geographically coincident with large clusters of severe EV-D68 infections. A second outbreak of AFM was reported two years later in 2016 in the US, with 149 confirmed cases across 39 states including the District of Columbia, again coincident with reports of large EV-D68 detections. Application of the

Bradford-Hill criteria concluded for the first time that EV-D68 was the likely the cause of the 2014 AFM outbreak (,).

In each intervening year, in 2015 and 2017, sporadic cases of AFM have been reported: 22 confirmed cases across 17 states, and 33 confirmed cases across 16 states respectively.

Unlike previous AFM outbreaks associated with EV-D68, this outbreak has been associated with both EV-A71 and EV-D68. Among 125 confirmed AFM cases tested, 21 (42%) have tested positive for EV-A71, 16 (32%) positive for EV-D68, and 13 (26%) positive for other viruses types included rhinovirus A subtypes and Coxsackie A viruses ( ). In some states, one species appears to predominate, such as in Colorado, where among 16 AFM cases, 11 tested positive for EV-A71, one for

Unusual features

EV-D68, and two negative for enterovirus species ( ).

Since 2014, there have been 512 confirmed cases of AFM in the US ( ). To-date, this is the largest outbreak of confirmed AFM in the US. The incidence of reported AFM has increased every two years since 2014 in the United States. Surveillance data shows 120 cases of confirmed AFM reported in 2014, 149 confirmed in 2016, and 193 in 2018 confirmed so far (,).

The number of states implicated in each outbreak has also increased from 34 in 2014 to 39 in both 2016/18 ( ). Reporting of AFM however remains voluntary in the US so the true incidence remains unknown. The clinical similarity of AFM to other neurologic syndromes, e.g. Guillain-Barre syndrome and idiopathic transverse myelitis, increases the chance of misdiagnosis, potentially concealing the true AFM incidence

Critical analysis

further ( ). Interestingly, the onset of the 2018 outbreak

coincides with time-of-onset observed in both previous outbreaks in 2014 and 2016: August to October ( ). This suggests a two-year cyclical dynamic of AFM outbreaks and a seasonal pattern is emerging, meaning another outbreak in August 2020 might also be expected. This cyclical dynamic also supports the role of a viral agent as the cause of the 2018 outbreak rather than unknown sporadic or environmental cause, such as a toxin. Supporting this conclusion, the CDC released a report on 16 November 2018 based on the results of early diagnostic testing stating "*clinical, laboratory, and epidemiologic evidence to date suggest a viral association*" ( ). Among 125 confirmed AFM cases tested, 21 (42%) have tested positive for EV-A71, 16 (32%) positive for EV-D68, and 13 (26%) positive for other viruses types, including rhinovirus A subtypes and Coxsackie A viruses ( ). Detection in the cerebrospinal fluid (CSF) is confirmative of the pathogen being the cause of AFM, however only two AFM cases among 21 specimens tested positive: one EV-A71, and another for EV-D68. While these numbers are limited, it is rare that EV-D68 and EV-A71 are detected in the CSF, even among cases with confirmed AFM and positive respiratory or stool samples. For example, in the 2014 outbreak, of the 120 confirmed AFM cases, only 12 had confirmed EV-D68 infections, 11 from respiratory samples, and one from CSF (,). This is likely due to the limited replication and persistence of EV virions in the CSF (, ,) and the delay between symptom onset and specimen sampling as observed in the 2014 outbreak ( ) .Therefore, while CSF positive detections are confirmatory,

negative CSF results does not weaken other clinical and diagnostic evidence for EV-A71 and EV-D68 aetiology. Due to the emergence of EV-D68 as a likely cause of the 2014/16 AFM outbreak in US, it is possible that EV-D68 may be the cause of the 2018 outbreak. Clinical and diagnostic evidence provided by the CDC above supports this conclusion. Perhaps unusual in this outbreak is the simultaneous detection of EV-A71 among many AFM cases. Detection of EV-A71 in previous AFM outbreaks in the US is not known. In 2014, 11 Non-EV-D68 enterovirus species were detected in the stool of AFM cases, suggestive of EV-A71 infection as a faecal-oral pathogen but was not specified ( ). In 2016, a single AFM case in Washington State tested positive for EV-A71 among 10 confirmed AFM cases ( ). Similarly, there is little evidence internationally for co-circulation of EV-D68 and EV-A71 among AFM cases. For example, in France, enterovirus-associated AFM appears mostly associated with EV-A71, although EV-D68 has been detected previously in a single case ( ). Of all the 38 states affected, Texas has recorded the most AFM cases (n=25), followed by Colorado (n=16). Based on public data and reporting, we cannot determine if the majority of confirmed cases in Texas had onset dates during the epidemic period August to October, or prior. In September, a Morbidity and Mortality Weekly Report (MMWR) was published describing an increase in EV-A71 associated encephalitis, meningitis and AFM in Colorado between May 10 and June 5, 2018 ( ). During this period, 34 young children (<2 years) presented with neurological symptoms and tested

positive for EV-A71; three were subsequently classified as AFM ( ). In the current epidemic which began in August, of the 16 positive AFM cases, 11 have tested positive for EV-A71 ( ). Only one cases has tested positive one for EV-D68, while two have tested negative for enterovirus species ( ). This might suggest EV-A71 is the predominate cause of the current AFM outbreak in Colorado, while EV-D68 is only a minor cause there.

In 2014, like 2018, Colorado was also one of the first states to report an increase in AFM detections ( ). This suggests Colorado may be a significant state for the emergence of AFM epidemics in the US. It is unclear if other states also experience simultaneous emergence of AFM or if a single state such as Colorado may act as a source, potentially disseminating the disease across the US. If the emergence is simultaneous, the environment and seasonality of non-polio enteroviruses may provide one explanation. Non-polio enteroviruses are known to circulate all-year round, however peaks typically occur in summer between July and September in the Northern Hemisphere ( ). Outbreak timing and transmission intensity has been shown to be associated with latitudes and dew-point temperatures such that northern states observed peaks later in the season whereas southern states observed a regular distribution of cases throughout the year. This supports the case for non-polio enteroviruses as the cause of the current AFM outbreak as most states affected since August epidemic wave are located in the Northern US: Washington, Illinois, Colorado, Minnesota, New Jersey, Pennsylvania, and Ohio ( ). Clusters

of EV-D68 have also been reported in New York, however none of these cases have exhibited symptoms associated with AFM ( ). Other evidence suggests non-polio enterovirus seasonality may be driven by a waning of seroprevalence in the population and the emergence of immunologically naïve newborns ( ).

The detection of 13 non-enterovirus species among AFM cases ( ) means other known viral aetiologies might also be implicated, including rhinovirus A subtypes and Coxsackie A viruses, however they do not have a history of neurological invasion and AFM. Likewise, symptomatic evidence can exclude flaviviruses previously associated with AFM such as West Nile Virus, which typically present with skin rash, as the cause of this AFM outbreak. Furthermore, diagnostic testing for flaviviruses require blood samples, which if taken, have not been publicly reported. Adenoviruses type 21 (AD21) has also been associated with AFM in the past ( ). A large outbreak of Adenovirus has sickened 36 in New Jersey between September and November, which has temporal and spatial associations with current AFM outbreaks also in New Jersey (,). Eleven deaths have been implicated in this Adenovirus outbreak, however no cases have developed AFM and the dominant clinical syndrome was reported to be respiratory illness ( ). Typing has also shown a mix of adenoviruses types 3 and 7 predominating in the New Jersey outbreak, which do not have a history of causing AFM ( ). This might practically eliminate AD21 as a potential cause of the current AFM outbreak.

Key questions

What is the cause of AFM in the US in 2018?

Why is AFM increasing in the US?

Is Colorado a key state for the emergence of AFM epidemics in the US or is the seasonality of non-polio enteroviruses a key predictor?

Is EV-D68 or EV-A71 the primary cause of this AFM epidemic, and if so, how common is it for two different co-circulating viruses to cause a single outbreak?

Is there common factor among all cases with positive and negative enterovirus results?

Is there another non-enterovirus related cause to this outbreak? Could Rhinovirus A and Coxsackie A viruses be a new cause of AFM?

Can we exclude flaviviruses (West Nile, Saint Louis encephalitis virus, and Japanese encephalitis virus), other adenoviruses or a new pathogen?

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EXHIBIT NO.

22

Joe Scarborough on defending Trump: "if you support him, you are" racist

"He will forever be remembered as the president who traumatized little children," co-host Mika Brzezinski said

Travis Gettys JUNE 23, 2018 9:58AM SALLON.COM

MSNBC's Joe Scarborough and Mika Brzezinski tore into "openly racist" President Donald Trump and his supporters over his intentionally cruel family separation policy.

The "Morning Joe" co-hosts said the president was trying to back away from a disaster of his own making, and Scarborough said Trump's intentions were perfectly clear — and morally indefensible.

"You've got Charlottesville, where Donald Trump of course defended white supremacists with moral equivalency," Scarborough said. "Even this year, Donald Trump calling Hispanics 'breeders.' Just last week, saying that immigrants coming across the border were quote 'infesting America,' and no, he wasn't talking about gang members."

"You can talk again about him denying any knowledge of David Duke or the Ku Klux Klan," he continued. "(Trump supporters) cannot say, 'Oh, I'm just supporting him because he's giving them hell in Washington, D.C. No, he's been openly racist just like we said back in December of 2015, openly racist. If you support him, then you're supporting that, and you are that. It's that simple. That's what we've come to now."

Brzezinski shamed the president, his daughter and everyone close to the White House for ripping apart immigrant families for cynical purposes.

EXHIBIT NO.

23

Surveillance for Acute Flaccid Myelitis - United States, 2018-2022

Erin R Whitehouse, Adriana Lopez, Randall English, Halle Getachew, Terry Fei Fan Ng, Brian Emery, Shannon Rogers, Sarah Kidd

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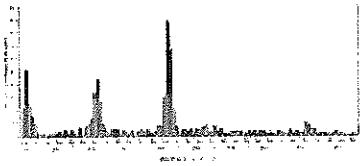
Abstract

Acute flaccid myelitis (AFM) is a serious neurologic condition primarily affecting children; AFM can cause acute respiratory failure and permanent paralysis. AFM is a rare but known complication of various viral infections, particularly those of enteroviruses (EVs). Increases in AFM cases during 2014, 2016, and 2018 were associated with EV-D68 infection. This report examines trends in confirmed AFM cases during 2018-2022 and patients' clinical and laboratory characteristics. The number of AFM cases was low during 2019-2022 (28-47 cases per year); the number of cases remained low in 2022 despite evidence of increased EV-D68 circulation in the United States. Compared with cases during the most recent peak year (2018), fewer cases during 2019-2021 had upper limb involvement, prodromal respiratory or febrile illness, or cerebrospinal fluid pleocytosis, and more were associated with lower limb involvement. It is unclear why EV-D68 circulation in 2022 was not associated with an increase in AFM cases or when the next increase in AFM cases will occur. Nonetheless, clinicians should continue to suspect AFM in any child with acute flaccid limb weakness, especially those with a recent respiratory or febrile illness.

Conflict of interest statement

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

Figures



FIGURE

Confirmed cases of acute flaccid myelitis,...

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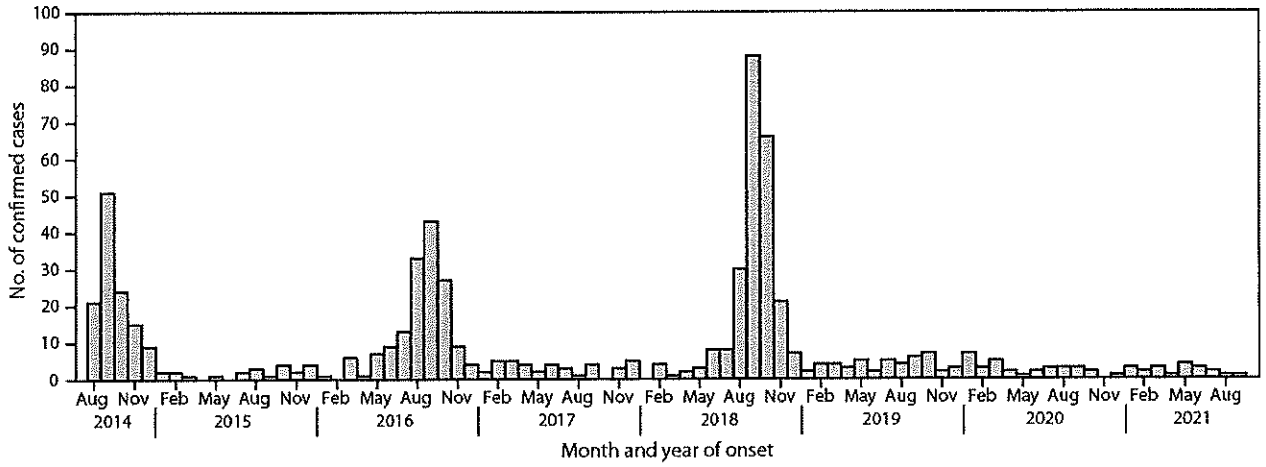
EXHIBIT NO.

24

FIGURE. Confirmed cases of acute flaccid myelitis (N = 670), by month of onset — United States, August 2014–September 2021*



* As of October 23, 2021.

EXHIBIT NO.

25

DHS Issues A New Memo to Terminate MPP

Release Date: October 29, 2021

WASHINGTON – Secretary of Homeland Security Alejandro N. Mayorkas today issued a new memorandum announcing and explaining his decision to terminate the Migrant Protection Protocols (MPP) program.

"This Administration is tackling longstanding problems that have plagued our immigration system for decades in order to achieve needed systemic change. MPP does not help meet this goal," **said Secretary Mayorkas.** "MPP had endemic flaws, imposed unjustifiable human costs, pulled resources and personnel away from other priority efforts, and did not address the root causes of irregular migration. MPP not only undercuts the Administration's ability to implement critically needed and foundational changes to the immigration system, it fails to provide the fair process and humanitarian protections that individuals deserve under the law."

Secretary Mayorkas conducted an extensive review to assess whether MPP should be maintained, terminated, or modified. He studied court documents, relevant data, internal reviews, and publicly available materials, and met with a broad and diverse array of internal and external stakeholders, including DHS personnel as well as state and local officials and community leaders across the country. Secretary Mayorkas concluded that the benefits do not justify the costs, particularly given the way in which MPP detracts from other regional and domestic goals and policy initiatives that better align with this Administration's values. MPP distracts from efforts to achieve regional solutions that address the root causes driving migrants to leave their countries and that tackle this challenge before vulnerable individuals have taken the perilous journey to our border.

"We must invest in durable policies that disincentivize irregular migration while promoting safe, orderly, and humane pathways," **continued Mayorkas.** "In addition to developing enduring, regional solutions with partner nations, we must address problems that have plagued our asylum system for years."

The Administration, for example, has designed the Dedicated Docket that enables immigration judges to adjudicate cases within 300 days, and is promulgating a forthcoming Asylum Officer Rule, which will transfer the initial responsibility for adjudicating asylum claims from immigration judges to USCIS asylum officers to produce timely and fair decision-making. These reforms are expected to yield transformative and lasting changes to the asylum system. Once fully implemented, these policies will address migratory flows more effectively than MPP, while holding true to our nation's values.

The Administration remains under a court order requiring it to reimplement MPP in good faith, which it will abide by even as it continues to vigorously contest the ruling. As part

of these efforts, DHS is engaged in ongoing and high-level discussions with Mexican government and has issued contracts to build temporary court facilities in Texas. MPP cannot be reimplemented, however, unless and until the Government of Mexico makes an independent decision to accept returns under the program.

The termination of MPP will not take effect until the current injunction is lifted.

The Department remains committed to building a safe, orderly, and humane immigration system that upholds our laws and values. The Department also continues to process individuals in accordance with U.S. law and our mission.